

Remarks

I. Status Of The Claims And Support For The Amendments

Claims 1-3, 5, 7, 8, 11, 12, 14-16, 18, 20, 23 and 24 have been amended. Of the elected claims, Claims 10, 21 and 22 have been canceled. Non-elected Claims 25-39 have been canceled, and Applicants reserve the right to file one or more divisional applications to the subject matter therein. Claims 1-9, 11-20, 23 and 24 are pending in this application.

The Specification has been amended to recite trademarks in the upper case.

Claim 1 has been amended to further clarify Applicants' invention. Support for the amendment of Claim 1 is found in the Specification at page 20, paragraphs [0073] and [0076]; page 23, paragraphs [0085] to [0087]; page 31, last line to page 32, first two lines (paragraph 0121)); page 34, paragraph [0131]; Figure 6; page 38, paragraphs [0147] and [0148]; and original Claim 10.

A typographical error has been corrected in Claim 8. A minor grammatical error has been corrected in Claim 15. Claim pendency has been changed in Claims 11, 12 , 14, 20 and 23.

Support for the amendment of Claim 18 is found in Claim 17.

Support for the amendment of Claim 24 is found in Claim 1.

No new matter has been added by these amendments.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider and withdraw all of the outstanding objections and rejections.

II. Description of the Invention

The present invention provides a method for producing a biomolecule of interest in a host cell that is not secreted by the host cell, comprising the steps of

a) cultivating host cells to produce the biomolecule of interest and optionally harvesting and resuspending the cells to form a cell suspension,

b) disintegrating the cells by alkaline lysis by contacting the cell suspension with an alkaline lysis solution and allowing the cell suspension and the alkaline lysis solution to flow through a lysis reactor that is filled with particulate material, thereby forming a lysed cell solution,

c) precipitating the cell debris and impurities by neutralizing the lysed cell solution in a neutralization reactor to form a mixture comprising a precipitate and a lysate,

d) separating the lysate from the precipitate, wherein the mixture comprising the precipitate and the lysate is allowed to flow downward through a clarification reactor that is partially filled with retention material to form a retention layer, whereby the precipitate is retained on top of and within the retention layer and the cleared lysate leaves the reactor through the bottom of the reactor, and

e) purifying the biomolecule of interest,

wherein the lysis reactor is directly connected to the neutralization reactor, and wherein the neutralization reactor is directly connected to the clarification reactor.

In the claimed method, the lysis reactor is directly connected to the neutralization reactor, such that the lysed cell solution is transported from the lysis reactor to the neutralization reactor via a direct connection. In addition, the neutralization reactor is

directly connected to the clarification reactor, such that the precipitate and lysate are transported from the neutralization reactor to the clarification reactor via a direct connection.

III. Objections to the Specification

At page 3 of the Office Action, the Examiner noted that certain trademarks discussed in the Specification should be capitalized. The Specification has been amended to recite the trademarks in the upper case.

The Examiner also noted certain spelling errors in paragraph [0040] of the published application (corresponding to paragraph [0035] in the application as filed). These spelling errors have been corrected.

As a result of the amendment of the Specification, it is believed that these objections are moot. Applicants respectfully request that these objections be reconsidered and withdrawn.

IV. Objections to the Claims

At page 3 of the Office Action, the Examiner objected to claim 8, because of a spelling error. The spelling error has been corrected. As a result of the amendment of Claim 8, it is believed that this objection is moot. Applicants respectfully request that this objection be reconsidered and withdrawn.

V. The Rejection Under 35 U.S.C. § 112 Should Be Withdrawn

Claims 1-24 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants respectfully traverse this rejection.

Claims 10, 21 and 22 have been canceled.

It is the Examiner's view that in Claims 1 and 11, the term "gently" is unclear. To expedite prosecution, and without acquiescing to the rejection, the term "gently" has been deleted from claims 1 and 11.

It is also the Examiner's view that in Claim 1, the phrase "reactor that is partially filled, in its lower part" is unclear. To expedite prosecution, and without acquiescing to the rejection, Claim 1 has been amended to recite "reactor that is partially filled with retention material to form a retention layer."

In Claim 7, the Examiner objected to the phrase "the process," as lacking antecedent basis. Claim 7 has been amended to delete the phrase to which the Examiner objects.

In Claim 16, the Examiner objected to the phrase "transportation between step b) and d)." To expedite prosecution, and without acquiescing to the rejection, Claim 16 has been amended to delete the term to which the Examiner objects.

In Claim 23, the Examiner objected to the phrase "by being connected to." To expedite prosecution, and without acquiescing to the rejection, Claim 23 has been amended to delete the term to which the Examiner objects.

In Claim 24, the Examiner objected to the phrase "the cell mass." To expedite prosecution, and without acquiescing to the rejection, Claim 24 has been amended to

recite “[t]he method of claim 1, wherein the host cells obtained in step a) are cryo-pelleted.”

It is believed that as a result of these claim amendments, the alleged grounds for this rejection are moot. Applicants respectfully request that this rejection be reconsidered and withdrawn.

VI. The Rejections Under 35 U.S.C. § 102 Should Be Withdrawn

A. The Rejection Over QIAGEN Should Be Withdrawn

Claims 1, 2, 5, 7-9, 15, 17, 19 and 20 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by The QIAGEN[®] Transfection Source Book, 1999, pages 15 and 48-55 (“QIAGEN”). Applicants respectfully traverse this rejection.

Claim 1 has been amended to recite that the lysis reactor is directly connected to the neutralization reactor, and that the neutralization reactor is directly connected to the clarification reactor. QIAGEN fails to teach such a structure. Therefore, QIAGEN fails to teach the method of Claim 1.

Claims 2, 5, 7-9, 15, 17, 19 and 20 depend, directly or indirectly, from Claim 1, and thus incorporate the limitations of Claim 1. For the same reasons that QIAGEN fails to teach the method of Claim 1, QIAGEN fails to teach the method of Claims 2, 5, 7-9, 15, 17, 19 and 20.

Applicants respectfully request that this rejection be reconsidered and withdrawn.

B. The Rejection Over Gonzales Should Be Withdrawn

Claims 1-5, 9, 15 and 19-21 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Gonzales, U.S. Patent No. 5,783,686 (“Gonzales”). Applicants respectfully traverse this rejection.

Claim 21 has been canceled.

At column 7, lines 26-50, Gonzales discusses the use of a Biomek automated workstation. A Biomek workstation is a fluid handling robot that pipettes solutions. That is different from the claimed method, in which the lysis reactor is directly connected to the neutralization reactor, such that the lysed cell solution is transported from the lysis reactor to the neutralization reactor via a direct connection. In addition, in the claimed method, the neutralization reactor is directly connected to the clarification reactor, such that the precipitate and lysate are transported from the neutralization reactor to the clarification reactor via a direct connection.

Gonzales fails to teach a method for producing a biomolecule of interest, in which the lysis reactor is directly connected to the neutralization reactor, or in which neutralization reactor is directly connected to the clarification reactor. Therefore, Gonzales fails to teach the method of Claim 1.

Claims 2-5, 9, 15, 19 and 20 depend, directly or indirectly, from Claim 1, and thus incorporate the limitations of Claim 1. For the same reasons that Gonzales fails to teach the method of Claim 1, Gonzales fails to teach the method of Claims 2-5, 9, 15, 19 and 20.

Applicants respectfully request that this rejection be reconsidered and withdrawn.

C. The Rejection Over Marquet Should Be Withdrawn

Claims 1, 2, 5, 6, 9, 15 and 17-21 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Marquet *et al.*, WO 95/21250 ("Marquet"). Applicants respectfully traverse this rejection.

Claim 21 has been canceled.

Marquet fails to teach a method for producing a biomolecule of interest, in which the lysis reactor is directly connected to the neutralization reactor, or in which neutralization reactor is directly connected to the clarification reactor. Therefore, Marquet fails to teach the method of Claim 1.

Claims 2, 5, 6, 9, 15 and 17-20 depend, directly or indirectly, from Claim 1, and thus incorporate the limitations of Claim 1. For the same reasons that Marquet fails to teach the method of Claim 1, Marquet fails to teach the method of Claims 2, 5, 6, 9, 15 and 17-20.

Applicants respectfully request that this rejection be reconsidered and withdrawn.

VII. The Rejections Under 35 U.S.C. § 103 Should Be Withdrawn

A. The Rejection Over QIAGEN In View Of Craig Should Be Withdrawn

Claims 1 and 24 stand rejected under 35 U.S.C. § 103 as allegedly obvious over QIAGEN in view of Craig, U.S. patent No. 6,381,967 ("Craig"). Applicants respectfully traverse this rejection.

Craig fails to suggest that the manual method for purifying nucleic acid in QIAGEN be altered such that the lysis reactor is directly connected to the neutralization reactor, so that the lysed cell solution is transported from the lysis reactor to the

neutralization reactor via a direct connection. Moreover, Craig fails to suggest that the manual method of QIAGEN be modified such that the neutralization reactor is directly connected to the clarification reactor, so that the precipitate and lysate are transported from the neutralization reactor to the clarification reactor via a direct connection.

Even in combination, QIAGEN and Craig would not have suggested the method of Claims 1 and 24. Applicants respectfully request that this rejection be reconsidered and withdrawn.

B. The Rejection Over Gonzales In View Of Craig Should Be Withdrawn

Claims 1 and 24 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Gonzales in view of Craig. Applicants respectfully traverse this rejection.

Craig fails to suggest that the method for purifying nucleic acid in Gonzales be altered such that the lysis reactor is directly connected to the neutralization reactor, so that the lysed cell solution is transported from the lysis reactor to the neutralization reactor via a direct connection. Moreover, Craig fails to suggest that the method of Gonzales be modified such that the neutralization reactor is directly connected to the clarification reactor, so that the precipitate and lysate are transported from the neutralization reactor to the clarification reactor via a direct connection.

Even in combination, Gonzales and Craig would not have suggested the method of Claims 1 and 24. Applicants respectfully request that this rejection be reconsidered and withdrawn.

C. The Rejection Over Marquet In View Of Craig Should Be Withdrawn

Claims 1 and 24 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Marquet in view of Craig. Applicants respectfully traverse this rejection.

Craig fails to suggest that the method for purifying nucleic acid in Marquet be altered such that the lysis reactor is directly connected to the neutralization reactor, so that the lysed cell solution is transported from the lysis reactor to the neutralization reactor via a direct connection. Moreover, Craig fails to suggest that the method of Marquet be modified such that the neutralization reactor is directly connected to the clarification reactor, so that the precipitate and lysate are transported from the neutralization reactor to the clarification reactor via a direct connection.

Even in combination, Marquet and Craig would not have suggested the method of Claims 1 and 24. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the presently outstanding objections and rejections. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully
requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

A handwritten signature in black ink, appearing to read "Ann E. Summerfield".

Ann E. Summerfield
Attorney for Applicants
Registration No. 47,982

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1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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